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2. Patent application number
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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — Switzerland

4. Title of the invention — A PHARMACEUTICAL COMPOSITION

5. Name of your agent *(if you have one)* — W. H. Beck, Greener & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Patents ADP number *(if you know it)* — 323001 — 08991754001

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Continuation sheets of this form	
Description	9
Claim(s)	4
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Request for a preliminary examination and search (Patents Form 9/77)	
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11. I/We request the grant of a patent on the basis of this application.

Signature(s) W.H. Beck, Greener & Co Date 13.02.04

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

Dr. James Stones - (020) 7693 5600

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DUPLICATE

A PHARMACEUTICAL COMPOSITION

The present invention relates to a soft gelatin capsule and, in particular, to a soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof.

Gelatin is a heterogeneous mixture of water-soluble proteins of high molecular weight extracted from a number of sources of collagen such bovine bones and hide, pig skin or fish skin. Broadly speaking, there are two types of gelatin, Type A gelatin and Type B gelatin, depending on the method of extraction.

According to "Gelatin Processing" (US National Organic Standards Board Technical Advisory Panel Review; 1st March 2002), Type A gelatin is extracted following an acid pre-treatment process and porcine gelatin is usually extracted in this way. Pigskins are dehaired and degreased and the resultant skin is passed through a chopper or macerator to cut the skin into uniform sizes. The skin is then soaked at a pH of 1 to 4 with a food-grade mineral acid such as hydrochloric acid, phosphoric acid or sulphuric acid for 8 to 30 hours. The acid-treated pigskin is then washed with water to remove impurities and extracted with hot water. The extract is filtered through an anion-cation exchange column to reduce ash or mineral levels. The gelatin extract is vacuum concentrated or ultra filtered to a concentration between 15 to 35 %, filtered, pH adjusted to between 3.5 and 6. and evaporated to 50 % solids. The residue is chilled, extruded, dried and milled to the required particle size and then packaged. It is also known to pre-treat bovine ossein (de-mineralised bone) with acid prior to extraction of the gelatin although bovine ossein is more commonly pre-treated with alkali.

Type B gelatin is extracted following an alkali pre-treatment process and bovine gelatin is usually extracted in this way (*ibid*). Bones are crushed, cooked, centrifuged and dried. The extracted bone is degreased prior to gelatin extraction and de-mineralised with 4 to 6 % hydrochloric acid for a period of 5 to 7 days. The ossein is washed repeatedly with water to remove impurities and then treated with 1 to 4 % lime (calcium hydroxide) slurry to adjust the pH to about 12 for periods of 35 to 70

days with agitation and weekly lime changes to remove non-collagen components. The ossein is then washed and mineral acid is added to neutralise excess lime and adjust the pH to 3. The final pH after all wash operations is between 5 and 7. De-mineralised hot water is then used to extract the gelatin. The liquid gelatin solution may be filtered through a cellulose/diatomaceous earth plate and frame filter and deionised using an anionic-cationic resin bed. The resin solution is evaporated to a concentration between 15 to 45 %. The concentrated gelatin is filtered, pH adjusted to between 5 and 7, sterilised, cooled and air-dried. It is then milled to the required size and packaged. The alkaline process may take up to 20 weeks.

Gelatin is used, for example, to encapsulate various foods and nutritional supplements but especially medicines for oral administration to treat a number of conditions. Plasticizers such as glycerine may be added to gelatin to produce soft gelatin capsules. Formaldehyde and other aldehydes may be used to harden gelatin capsules and enable them to pass from the stomach to the intestines. The vast majority of soft gelatin capsules are manufactured from Type B, e.g. bovine, gelatin.

Omega-3 polyunsaturated fatty acids such as 5, 8, 11, 14, 17-eicosapentaenoic acid (or "EPA") or 4, 7, 10, 13, 16, 19-docosahexaenoic acid (or "DHA") are well known to be useful in the treatment of inflammatory bowel disease (or "IBD") (see, for example, EP-A-0244832, EP-A-0289204, EP-A-0311091 and WO-A-93/21912). WO-A-96/36329 (Buser *et al*; published on 21st November 1996) discloses a treatment of IBD involving oral administration of hard gelatin capsules containing a formulation that comprises a mixture of EPA and DHA. Each capsule is film coated with Eudragit™ NE 30-D which is an enteric material comprising poly(ethylacrylate-methylmethacrylate) having an average molecular weight of about 800,000. The capsules pass through the stomach and then disintegrate and release the contents in the small intestine. Results indicate that clinical relapses in Crohn's disease may be prevented by the oral administration of such coated capsules.

It is disclosed in US-A-2870062 (Scherer *et al*; published on 20th January 1959) that "standard gelatin capsules" disintegrate in contact with deliquescent or hygroscopic chemicals, such as liquid non-ionic detergents, salts of strong acids and

bases, choline chloride and chloral hydrate, encapsulated within. US-A-2870062 discloses the use of capsules made from specially selected low viscosity, high Bloom strength gelatin prepared from acid treated bone precursor. Such capsules do not appear to disintegrate when left in contact with deliquescent or hygroscopic chemicals.

EP-A-0100052 (Yu; published on 8th February 1984) discloses soft gelatin capsules containing PGE-type prostaglandin fatty acid compositions. Comparative studies appear to indicate that soft gelatin capsules made from Type B gelatin accelerate degradation of the prostaglandin composition whereas soft gelatin capsules made from Type A gelatin retain the stabilising effect of the solvent in which the prostaglandin fatty acids are dissolved.

The inventors have discovered that, under certain conditions, soft gelatin capsules made from Type B gelatin and containing a pharmaceutical formulation comprising omega-3 polyunsaturated fatty acids can harden over time, even in the presence of plasticizers in the gelatin and have concluded that the hardening is due to chemical interaction between the omega-3 polyunsaturated fatty acid formulation and the gelatin itself. Such a hardening effect can reduce the shelf life of the capsules as, when the hardened capsules are administered orally, they pass not only through the stomach but also though the small intestine and may even pass through a substantial part of the large intestine before the capsule disintegrates and the pharmaceutical formulation is released. If the capsules are being administered as a treatment of IBD then release of the omega-3 polyunsaturated fatty acid formulation beyond the small intestine will not be effective in this treatment. It is, therefore, an object of preferred embodiments of the present invention to provide a soft gelatin capsule containing an omega-3 polyunsaturated fatty acid formulation that displays a reduced hardening rate and thereby has an increased shelf life when compared to existing soft gelatin capsules containing omega-3 polyunsaturated fatty acids.

Disintegration of a soft gelatin capsule *in vivo* occurs not only though dissolution in an aqueous medium but also through the action of proteases on the gelatin. However, the chemical interaction between the omega-3 polyunsaturated fatty acid and the gelatin is uncontrolled and may continue throughout the shelf life of

the product. In addition, a coating on the capsule will usually hinder the action of the proteases thereby reducing their effectiveness.

According to a first aspect of the present invention, there is provided a soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof characterised in that the capsule comprises gelatin extracted by an extraction process comprising acid pre-treatment of a collagen source.

One advantage of this type of soft gelatin capsule is that the rate of hardening is significantly less than that for existing soft gelatin capsules (containing an omega-3 polyunsaturated fatty acid formulation) comprising gelatin extracted by an extraction process comprising alkali pre-treatment of a collagen source. The reduced rate of hardening translates into an increased shelf life for the capsules. A further advantage is that it is possible to move away from gelatin made from bovine bones and hides. In recent years, there has been some concern regarding the possible transmission of spongiform encephalopathies such as bovine spongiform encephalopathy (or "BSE") to humans. Type A gelatin, or gelatin extracted by an extraction process comprising acid pre-treatment of a collagen source, is usually made from pig skin and, thus, the use of such gelatin for the manufacture of soft gelatin capsules avoids any risk of contracting BSE from bovine Type B gelatin.

The decrease in hardening rate is surprising and unexpected as porcine gelatin (usually Type A gelatin) and bovine gelatin (usually Type B gelatin) have basically the same chemical structure in that the amino acid residues in both types of gelatin are essentially identical. Therefore, the skilled person would not expect the two types of gelatin to interact differently with the same omega-3 polyunsaturated fatty acid.

The omega-3 polyunsaturated fatty acid is preferably present in the form of the free acid. However, pharmacologically acceptable derivatives may also be used. Examples of suitable derivatives include triglycerides, esters (such as ethyl ester), amides, complexes (e.g. with bile salts, cholesterol or chitosan) and salts (such as sodium or potassium salts). In preferred embodiments, the formulation consists

essentially of at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof.

Preferably, the formulation comprises 5, 8, 11, 14, 17-eicospentenoic acid (or "EPA"). EPA may present in an amount of at least about 50 wt % and preferably between from about 50 wt % to about 60 wt % of the formulation although it may also be desirable to have EPA present in an amount of at least about 90 wt % of the formulation for certain applications and/or to minimise the number of capsules needed to be taken to provide a therapeutically active dose.

The formulation may comprise 4, 7, 10, 13, 16, 19-docosahexaenoic acid (or "DHA"). DHA may be present in an amount of between from about 20 wt % to about 30 wt % of the formulation.

The soft gelatin capsule preferably comprises between from about 100mg to about 2000mg of said formulation. At present, two embodiments of the capsule are preferred, the first embodiment comprising about 500mg of said formulation and intended for use, for example, with children and the second embodiment comprising about 1000mg intended for adult use.

The gelatin used is preferably at least one selected from the group consisting of porcine gelatin, bovine gelatin and fish gelatin, provided that the gelatin has been extracted by an extraction process comprising acid pre-treatment of the relevant collagen source. Mixtures of these gelatins may also be used.

In certain preferred embodiments, the soft gelatin capsule will be used to treat IBD or Crohn's disease. In these embodiments, the capsule preferably delays release of the formulation until after passage through the stomach. Release preferably occurs after passage beyond the pancreatic duct in the duodenum and, more preferably, in the ileum. Preferably, release should not occur after the mid-jejunum. Release is typically delayed for at least 30 minutes after oral administration and preferably for between 30 to 60 minutes at pH 5.5. Release of the formulation begins after the integrity of the capsule wall is compromised, i.e. after dissolution or perforation of the gelatin wall. If release occurs due to the gelatin capsule becoming porous, then

release may also be sustained which may be advantageous, especially in the treatment of IBD or Crohn's disease.

Release may be delayed by coating the capsule with at least one enteric material that is resistant to dissolution in a time dependent and/or pH dependent manner. Alternatively or additionally, at least one such enteric material is integrated within the gelatin of the capsule. A preferred enteric material is a neutral polyacrylate such as poly(ethylacrylate-methylmethacrylate), especially Eudragit NE 30-D (Röhm Pharma GmbH) which has an average molecular weight of about 800,000.

According to a second aspect of the present invention, there is provided use of gelatin extracted by an extraction process comprising acid pre-treatment of a collagen source in the manufacture of a medicament comprising at least one soft gelatin capsule as defined in the first aspect for the oral treatment or prophylaxis of inflammatory bowel disease ("IBD") or Crohn's disease. The medicament may comprise at least one soft gelatin capsule having any of the preferred features discussed above in any appropriate combination.

According to a third aspect of the present invention, there is provided a process for the manufacture of a soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof, said process comprising encapsulating said pharmaceutical formulation in gelatin extracted by an extraction process comprising acid pre-treatment of a collagen source.

According to a fourth aspect of the present invention, there is provided use of gelatin extracted by an extraction process comprising acid pre-treatment of a collagen source in a soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof to improve resistance of the soft gelatin capsule to chemical interaction with the formulation. Preferably, said resistance is greater than that of a soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof in which the gelatin consists essentially of gelatin

extracted by an extraction process comprising alkali pre-treatment of a collagen source.

According to a fifth aspect of the present invention, there is provided use of gelatin extracted by an extraction process comprising acid pre-treatment of a collagen source in a soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof to improve shelf life of the soft gelatin capsule. Preferably, said shelf life is greater than that for a soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof in which the gelatin consists essentially of gelatin extracted by an extraction process comprising alkali pre-treatment of a collagen source.

The soft gelatin capsule may be used in the treatment or prophylaxis of IBD and, in particular, Crohn's disease. In such treatment, the daily dosage of the formulation would be set by the doctor in charge of the patient and would depend on a number of factors such as age. Usually, between from about 1g to about 8g of the formulation is administered to the patient per day. Administration may be in the form of a plurality of soft gelatin capsules according to the first aspect of the present invention. The total number of capsules administered daily will depend on the amount of the formulation in each capsule. Thus, for example, a daily dose of 4g of formulation might be administered in the form of either 8 500mg capsules or 4 1000mg capsules and a daily dose of 8g of formulation might be administered in the form of 8 1000mg capsules.

According to a sixth aspect of the present invention, there is provided a method of treatment or prophylaxis of IBD or Crohn's disease comprising administering between from about 1g to about 8g of a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable salt thereof per day in the form of a plurality of soft gelatin capsules according to the first aspect of the present invention. The capsules may have any of the preferred features discussed above in any appropriate combination.

The following is a description, by way of example only, of a presently preferred embodiment of the present invention.

Type A gelatin capsules were formed and simultaneously filled with an omega-3 polyunsaturated fatty acid formulation in a known manner. Type A porcine gelatin powder was mixed with water and plasticizer and then heated to form a molten gelatin mass. Two thin ribbons of the molten gelatin were produced and passed between two die rolls which determined the shape of the capsules. The formulation was injected between the two gelatin ribbons just before the die rolls sealed the capsules together by application of heat and pressure. The resulting capsule was then dried to the required moisture content.

The stability of the Type A gelatin capsules produced in this manner was compared with that for the Type B gelatin capsules produced using the same process. Batches of both capsules were stored for different periods (3 months, 6 months, 9 months and 12 months) and at different temperatures (25°C, 30°C and 40°C) and then the disintegration times of the capsules in purified water at 37°C according to Ph. Eur. were measured. The results are indicated in Table 1.

TABLE 1

Capsule	Storage Temp (°C)	0 months	3 months	6 months	9 months	12 months
Type B gelatin (Bovine)						
	25	7 min	9 min	9 min	6 min	10 min
	30	7 min	9 min	20 min	n.p.	Insoluble
	40	7 min	Insoluble	Insoluble	n.p.	n.p.
Type A gelatin (Porcine)						
	25	6 min	6 min	7 min	6 min	7 min
	30	6 min	7 min	8 min	n.p.	10 min
	40	6 min	8 min	10 min	n.p.	n.p.

It should take no longer than 30 min for a soft gelatin capsule to disintegrate if it is to release its contents effectively. Therefore, if a capsule failed to disintegrate in

30 min, it was deemed "insoluble". The term "n.p." indicated that the test was "not performed".

The results indicate that, for the Type B (bovine) gelatin capsules stored at a given temperature, there is a general increase in disintegration time as the storage time increases. In addition, for the Type B (bovine) gelatin capsules stored for a given time, there is a general increase in disintegration time as the storage temperature increases. These results are consistent with the omega-3 polyunsaturated fatty acid interacting chemically with the Type B gelatin resulting in a hardening of the capsule wall.

In contrast, disintegration time is not substantially increased for the Type A (porcine) gelatin capsules as either the storage time or storage temperature increases. These results would appear to indicate that the degree of hardening is significantly less for Type A (porcine) gelatin capsules than for Type B (bovine) gelatin capsules. In particular, attention is drawn to the disintegration results for the Type B (bovine) gelatin capsules stored at 30°C for 12 months and at 40°C for 3 months and 6 months as these capsules have been classified as "insoluble" whereas the corresponding Type A (porcine) gelatin capsules took no more than 10 minutes to dissolve.

It will be appreciated that the invention is not restricted to the details described above with reference to the preferred embodiments but that numerous modifications and variations can be made without departing from the spirit or scope of the invention as defined by the following claims.

CLAIMS

1. A soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof characterised in that the capsule comprises gelatin extracted by an extraction process comprising acid pre-treatment of a collagen source.

2. A soft gelatin capsule as claimed in Claim 1 wherein the formulation consists essentially of at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof.

3. A soft gelatin capsule as claimed in Claim 1 or Claim 2 wherein formulation comprises 5, 8, 11, 14, 17-eicosapentaenoic acid (or "EPA").

4. A soft gelatin capsule as claimed in Claim 3 wherein EPA is present in an amount of at least about 50 wt % of the formulation.

5. A soft gelatin capsule as claimed in Claim 3 or Claim 4 wherein EPA is present in an amount of between from about 50 wt % to about 60 wt % of the formulation.

6. A soft gelatin capsule as claimed in Claim 3 or Claim 4 wherein EPA is present in an amount of at least about 90 wt % of the formulation.

7. A soft gelatin capsule as claimed in any of the preceding claims wherein the formulation comprises 4, 7, 10, 13, 16, 19-docosahexaenoic acid (or "DHA").

8. A soft gelatin capsule as claimed in Claim 7 insofar as dependent from any of Claims 1 to 5 wherein DHA is present in an amount of between from about 20 wt % to about 30 wt % of the formulation.

9. A soft gelatin capsule as claimed in any of the preceding claims comprising between from about 100mg to about 2000mg of said formulation.

10. A soft gelatin capsule as claimed in any of the preceding claims comprising about 500mg of said formulation.

11. A soft gelatin capsule as claimed in any of Claims 1 to 9 comprising about 1000mg of said formulation.

12. A soft gelatin capsule as claimed in any of the preceding claims wherein the or at least one omega-3 polyunsaturated fatty acid is in free acid form or in the form of a pharmacologically acceptable salt thereof.

13. A soft gelatin capsule as claimed in any of the preceding claims wherein the omega-3 polyunsaturated fatty acid is in free acid form.

14. A soft gelatin capsule as claimed in any of the preceding claims wherein the gelatin comprises porcine gelatin.

15. A soft gelatin capsule as claimed in any of Claims 1 to 13 wherein the gelatin comprises bovine gelatin.

16. A soft gelatin capsule as claimed in any of Claims 1 to 13 wherein the gelatin comprises fish gelatin.

17. A soft gelatin capsule as claimed in any of the preceding claims wherein the capsule delays release of the formulation until after passage through the stomach.

18. A soft gelatin capsule as claimed in any of the preceding claims wherein the capsule delays release of the formulation until after passage beyond the pancreatic duct in the duodenum.

19. A soft gelatin capsule as claimed in Claim 17 or Claim 18 wherein the capsule is coated with at least one enteric material.

20. A soft gelatin capsule as claimed in any of Claims 17 to 19 wherein at least one enteric material is integrated within the gelatin of the capsule.

21. A soft gelatin capsule as claimed in Claim 19 or Claim 20 wherein the or at least one enteric material is a neutral polyacrylate polymer.

22. A soft gelatin capsule as claimed in any of Claims 19 to 21 wherein the or at least one enteric material is poly(ethylacrylate-methylmethacrylate).

23. Use of gelatin extracted by an extraction process comprising acid pre-treatment of a collagen source in the manufacture of a medicament comprising at least one soft gelatin capsule as defined in Claim 1 for the oral treatment or prophylaxis of inflammatory bowel disease ("IBD") or Crohn's disease.

24. Use as claimed in Claim 23 wherein the medicament comprises at least one soft gelatin capsule as defined in any of Claims 2 to 22.

25. A process for the manufacture of a soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof, said process comprising encapsulating said pharmaceutical formulation in gelatin extracted by an extraction process comprising acid pre-treatment of a collagen source.

26. Use of gelatin extracted by an extraction process comprising acid pre-treatment of a collagen source in a soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof to improve resistance of the soft gelatin capsule to chemical interaction with the formulation.

27. Use as claimed in Claim 26 wherein said resistance is greater than that of a soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof in which the gelatin consists essentially of gelatin extracted by an extraction process comprising alkali pre-treatment of a collagen source.

28. Use of gelatin extracted by an extraction process comprising acid pre-treatment of a collagen source in a soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof to improve shelf life of the soft gelatin capsule.

29. Use as claimed in Claim 28 wherein said shelf life is greater than that for a soft gelatin capsule containing a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof in which the gelatin consists essentially of gelatin extracted by an extraction process comprising alkali pre-treatment of a collagen source.

30. A method of treatment or prophylaxis of IBD or Crohn's disease comprising administering between from about 1g to about 8g of a pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable salt thereof per day in the form of a plurality of soft gelatin capsules as defined in Claim 1.

31. A method as claimed in Claim 30 wherein the soft gelatin capsules are as defined in any of Claims 2 to 22.

32. A soft gelatin capsule substantially as hereinbefore described with reference to the accompanying examples.

33. A process substantially as hereinbefore described with reference to the accompanying examples.

34. A use substantially as hereinbefore described with reference to the accompanying examples.

ABSTRACT

A PHARMACEUTICAL COMPOSITION

A pharmaceutical formulation comprising at least one omega-3 polyunsaturated fatty acid in free acid form or a pharmacologically acceptable derivative thereof is contained in a soft gelatin capsule characterised in that the capsule comprises gelatin extracted by an extraction process comprising acid pre-treatment of a collagen source. One advantage of the present invention over a soft gelatin capsule containing the same formulation but comprising gelatin extracted by an extraction process comprising alkali pre-treatment of the collagen source is that the present invention does not harden significantly over time and thus has a longer shelf life.